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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,764	09/10/2003	Norman B. Javitt	1049-1-032N	4851

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,764	JAVITT, NORMAN B.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04-24-2009 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 21 and 22 are pending. Claims 21 and 22 have been amended and claim 23-26 have been cancelled by Applicants' amendment filed on 04-24-2009.
3. Applicants elected to prosecute in the response filed on 02-22-2007 Group IV, claims 16-17 (now cancelled), drawn to a method of screening a compound capable of interfering with the expression of 27-hydroxy-7-dehydrocholesterol reductase activity. The election was treated as an election without traverse. Additionally, Applicants elected with traverse in the response to a supplemental restriction filed on 06-11-2007, the invention of Group II, claim 17, which is drawn to a method for identifying agents capable of interfering with the expression of 27-hydroxy-7-dehydrocholesterol reductase activity by measuring RNA expression. Note that amended claim 22 reads on measuring expression of MRNA CYP27 (e.g., CYP27 gene product is 27-hydroxylase) and not expression of 27-hydroxy-7-dehydrocholesterol reductase RNA. Generic claim 21 was previously examined to the

extent that it reads on the elected invention, i.e., drawn to a method for identifying agents capable of interfering with the expression of 27-hydroxy-7-dehydrochlosterol reductase activity.

4. Therefore, claims 21 and 22 are currently pending for examination to which the following grounds of rejection are applicable.

Response to arguments

Withdrawn Rejections/Objections in response to Applicant arguments or amendments

Specification

In view of Applicants' amendment of 12-14-2007 to the specification, at page 7, paragraphs [0026] [0027] and [0028] to reflect the content of figures 1-7, objection to the specification has been withdrawn.

Drawings

Applicant's amendment of 09-22-20008 to the drawings has been received. This corrects the deficiencies noted in the previous Office action.

Rejections/Objections maintained in response to Applicant arguments or amendments

Claim Rejections - 35 USC § 112-first paragraph-

Claim 22 remains rejected and claim 21 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide an enabling disclosure for identifying an agent compound capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol wherein said agent interferes with the expression of 27-hydroxy-7-dehydrochlosterol reductase activity , comprising determining the levels of 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol in the absence and presence of the compound and selecting a compound which increases 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol relative to levels in the absence of the agent.

The claims, when given the broadest possible interpretation, encompass *in vitro* or *in vivo* methods for identifying a compound that increases 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol merely by comparing levels of increased 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol in the presence and absence of said compound, wherein said compound interferes with expression levels of 27-hydroxy-7-dehydrochlosterol reductase activity, and selecting the compound increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol relative to levels of said sterols in the absence of the test compound. Claim 22 further limits the invention to a compound that does not alter a mRNA transcript of a CYP27 gene which encodes 27-hydroxylase. The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including how a test compound interferes with the activity of the 27-hydroxy-7-dehydrocholesterol reductase and how the unmodified expression profile of the CYP27 mRNA (CYP27 gene encodes 27-hydroxylase) correlates to the 27-hydroxy-7-dehydrochlosterol reductase activity have to be examined and considered for patentability

regarding the broadly claimed methods of screening for a test compound that increases 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol .

The specification as filed teaches plasma determination of oxysterol metabolites in Smith-Lemli-Opitz syndrome (SLOS) patients. Smith-Lemli-Opitz syndrome (SLOS) is a genetically determined disease resulting from a mutation in the gene encoding the 7-dehydrocholesterol 7-reductase (DHC7R) enzyme that converts 7-dehydrocholesterol to cholesterol (p. 3, paragraph [0010]). Thus mutation of a DHC7R enzyme results in increased level of 7-dehydrocholesterol (7-DHS). Moreover, the specification clearly identifies at page 28, paragraph [0095] that the concentration of both 27-hydroxy metabolites, 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol, were found to be markedly greater in SLOS samples than controls. Additionally, small amounts of 27-hydroxy-7-dehydrocholesterol could be detected in normal serum but not 27-hydroxy-8-dehydrocholesterol. Results appear to indicate that both 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlostero are downstream 27-oxydized products of accumulated 7**-dehydrocholesterol in** SLOS patients. Furthermore, 27-hydroxy-7-dehydrocholesterol was found to be effective down regulating cholesterol synthesis *in vitro,* by increasing rates of 7-dehydrochlosterol (7-DHS).

Indeed, the specification discloses that in fibroblast from SLOS patients wherein 27-hydroxy-7-dehydrocholesterol cannot be metabolized to 27-hydroxycholesterol because lack of 7-dehydrocholesterol 7-reductase enzyme, levels of 7-dehydrochlosterol (7-DHS), a cholesterol synthesis inhibitor, were increased in relation to control cultures (page 30, paragraph [0096]. In relation to the CYP27 gene product, the specification teaches that individuals with a genetic defect in producing 27-hydroxycholesterol exhibit accelerated atherosclerosis and die early in

life of severe coronary artery disease. The molecular basis of this genetic disease is a mutation in the CYP 27 gene, which results in a lack of cholesterol 27-hydroxylase activity (p2, paragraph [0005]). Note that 27- hydroxycholesterol is the CYP27 gene product. Moreover, the specification prophetically teaches how agents that inhibit 27-hydroxy-7-dehydrocholesterol-reductase are identified in a cell-free assay system (p. 24; paragraph 0085). However, Applicants have not provided sufficient disclosure in relation to the characterization of 27-hydroxy-7-dehydrocholesterol reductase, nor isolated the reductase enzyme, nor produced antibodies specific for recognizing the enzyme, nor isolated the cDNA of the enzyme from a library in order to show how a test agent may interfere with the activity of 27-hydroxy-7-dehydrocholesterol reductase. Applicants have not provided the nucleic acid sequence of such a reductase, or the oligo sequences of primers that might be used to detect how a compound interferes with 27-hydroxy-7-dehydrocholesterol reductase activity. Applicants have provided no nucleic acid sequences within the body of the specification, nor pointed to a Genbank or published article in which such sequences might appear. There is not description of which substrates are used by 27-hydroxy-7-dehydrocholesterol reductase or how 27-hydroxy-7-dehydrocholesterol reductase activity increases both 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol. There is not evaluation of direct 27-hydroxy-7-dehydrocholesterol reductase activity in any sample. Additionally, there is not guidance to effectively identify any compound able to increase levels of downstream products of such a 27-hydroxy-7-dehydrocholesterol reductase as 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol while preventing modification of the mRNA level of CYP27 encoding the 27 hydroxylase.

The art at the time the invention was made, teaches that hydroxylation of cholesterol by 7-α-hydroxylase leads to 7-hydroxylation C7α and production of 7 α-hydroxycholesterol to form primary bile acids by co-action of CYP7A and CYP7B (see, Lathe et al., 2002, Steroids, 967-97; p. 968; Specification, page 5, paragraph [0020]), However, there art is silent about how 7-hydroxylation by 7-hydroxylase leads into a pathway that generates 7-dehydrocholesterol and not 7- α-hydroxycholesterol, let alone a pathway by which 7-dehydrocholesterol is a substrate for 27- hydroxy-7-dehydrocholesterol reductase activity. In addition to 7-hydroxylation of cholesterol for bile formation, cholesterol can also be 27-hydroxylated for bile formation. For example, Honda et al., (1999, The Journal of Lipid Research, pp. 1520-1528,), using liver from SLOS model rats, teaches that rat mitochondrial sterol 27-hydroxylase catalyzed 27-hydroxylation of 7- and 8-dehydrocholesterols forming 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol that where were partially converted to 3ß-hydroxycholestadienoic acids (e.g., abnormal bile acids in SLOS) (p. 152, col. 1, paragraph 2). How much homology is there between the reductase of the instant claims and those known cholesterol 27-hydroxylases? Because applicants have provided no data on the existence of a 27-hydroxy-7-dehydrocholesterol reductase nor its specific substrate other than the identification of the 27-hydroxy-7- and 8-dehydrocholesterol downstream metabolites, the skilled artisan would have to perform trial and error in order to actually produce the enzyme, either in protein or nucleic acid form, to find its substrate products to test how a test compound specifically interferes with the activity of a 27-hydroxy-7-dehydrocholesterol reductase. Moreover, as 7- and 8-dehydrocholesterols are substrates of other mitochondrial enzymes such as sterol 27-hydroxylase, this would show that simply finding a difference in expression level of 27-hydroxy-7-dehydrochlosterol and 27-

hydroxy-8-dehydrochlosterol is not indicative of a compound that interferes with 27-hydroxy-7-dehydrocholesterol reductase activity in particular.

Response to Applicants' Arguments as they apply to rejection of 21 and 22 under 35 USC § 112- First paragraph- Enablement

At pages 6 and 7 of the remarks filed on 09-22-2008, Applicants essentially argue that: 1) as the claims have been amended to identify agent compounds based on the increase amount of 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol in the presence and absence of the compound there is not need to isolated and reproduce the 7-hydroxy-7-dehydrocholesterol reductase, and 2) One of skill in the art can readily and without undue experimentation determine the levels of CYP27 mRNA, 3) . The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), the instant invention is drawn to methods for identifying a test compound able to interfere with the activity of 27-hydroxy-7-dehydrocholesterol reductase by measuring increase levels of 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol. As substrates of 27-hydroxy-7-dehydrocholesterol reductase have not been identified in order to measure how a compound may interfere with the activity of 27-hydroxy-7-dehydrocholesterol reductase, and increase levels of 7-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol are not necessarily indicative of 27-hydroxy-7-dehydrocholesterol reductase activity because 7- and 8-dehydrocholesterols are substrates of other enzymes such as sterol 27-hydroxylase, for example, one of ordinary skill in the art would have to engage in undue experimentation to isolate and identify 27-hydroxy-7-dehydrocholesterol reductase, to determine its substrate and metabolites as well as its correlation to unmodified levels of mRNA CYP27

(e.g., gene encoding 27-hydroxylase) so as to effectively identify a compound able to increase 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol while interfering with the activity of identify 27-hydroxy-7-dehydrocholesterol reductase.

Regarding 2), the present issue of enablement is whether the scope of the patent protection sought by the Applicant as defined by the currently amended claims correlates with the scope of enabling disclosure set forth in the specification. In other words, is there enough disclosure for a method that identifies an agent compound that increases levels of 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol wherein said agent compound also interferes with activity of 27-hydroxy-7-dehydrocholesterol reductase? As 27 hydroxylation of 7- and 8-dehydrocholesterols is catalyzed by other enzymes and not merely by upstream 27-hydroxy-7-dehydrocholesterol reductase, does increase expression levels of these two oxidized sterols reflect on the biological activity of 27-hydroxy-7-dehydrocholesterol reductase?

Claim Rejections - 35 USC § 112- First paragraph- New Matter

Claims 21 and 22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Claim 21 recites a screening method for identifying agent compounds " wherein said compound interferes with the expression of 27-hydroxy-7-dehydrocholesterol reductase activity" and claim 22 recites "a compound capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol levels relative to the levels in the absence of the compound

and wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27, is not altered in the presence of the compound". The specification as filed teaches at page 1, paragraph [0005], that "a reduced level of 27-hydroxycholesterol in the serum was found to be associated with cholesterol build up in the tissues; thus, the administration of 27-hydroxycholesterol was proposed as a method for reducing the rate of cholesterol synthesis in the body… … . Individuals with a genetic defect in producing 27-hydroxycholesterol exhibit accelerated atherosclerosis and die early in life of severe coronary artery disease. The molecular basis of this genetic disease is a mutation in the CYP 27 gene, which results in a lack of cholesterol 27-hydroxylase activity". No other teachings are disclosed of "a compound capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol levels relative to the levels in the absence of the compound and wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27, is not altered". Thus is not clear that the Applicant was in possession of a genus of undefined methods comprising compounds "capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol levels wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27, is not altered" at the time the application was filed. Thus, the amended claims include impermissible New Matter.

Response to Applicants' Arguments as they apply to rejection of 21 and 22 under 35 USC § 112- First paragraph- New Matter

At pages 5 and 8 of Remarks, Applicants essentially allege that 1), support for the amendment to the claims may be found generally throughout the specification, and 2) the instant claims are drawn to screening methods for identifying agent compounds and not to a genus of

undefined compounds. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), Applicants have not indicated where support may be found for the above limitations regarding methods for identifying an agent compound able to increase 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol as recited in claims 21 and 21.

Regarding 2), the fact the invention is directed to a screening method for identifying an agent compound able to increase 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol and not to compounds is not disputed. However, the present issue of enablement is whether applicants have support of a genus of claimed methods for identifying an agent that increases 27-hydroxy-7-dehydrochlosterol and 27-hydroxy-8-dehydrochlosterol while interacting with the activity of 27-hydroxy-7-dehydrocholesterol reductase, wherein the expression of 27-hydrosylase, as determined by measuring its encoding mRNA CYP27, is not altered in the presence of the compound. A review of the specification as filed reveals no support for the claimed methods of identifying the claimed compounds.

Claim Rejections - 35 USC § 112

Claims 21 and 22 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is vague and indefinite in its recitation of "wherein said compound interferes with the expression of 27-hydroxy-7-dehydrocholesterol reductase activity". It is not apparent as to under what structural or functional parameters the interfering of expression by the agent compound is indicative of the activity of 27-hydroxy-7-dehydrocholesterol reductase. Is

expression of the mRNA transcript modified, expression at the protein level interfered with, affinity of the enzyme for its substrate modified by the agent compound? ". Because the 27-hydroxy-7-dehydrocholesterol reductase has not being isolated, nor the reductase enzyme activity determined, nor produced antibodies specific for recognizing the enzyme, nor isolated the cDNA of the enzyme from a library in order to show that applicants by measurement of mRNA level, the metes and bounds of the claim are not clearly set forth.

Claim 22 is indefinite insofar as they depend from claim 21.

New Grounds of Objection

Claim objection

Claims 21 and 22 are objected to because of the following informalities. Claim 21 recites the term "and/or" in line 2. It is unclear what the metes and bounds of this term, as "and" could be interpreted to include agents that only increase 27-hydroxy-7-dehydrocholesterol (cholesta-5,7-diene-3β-27 diol), or agents that increase both 27-hydroxy-7-dehydrocholesterol and 27-hydroxy-8-dehydrocholesterol or, "or" would imply that the 27-hydroxy-7-dehydrocholesterol and 27-hydroxy-8-dehydrocholesterol are increased by an agent in the alternative. Appropriate correction is requested

Conclusion

Claims 21 and 22 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/
Maria Leavitt, PhD
Examiner, Art Unit 1633